Articles

A new variant of Creutzfeldt-Jakob disease in the UK

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Summary

Background Epidemiological surveillance of Creutzfeldt-Jakob disease (CJD) was reinstituted in the UK in 1990 to identify any changes in the occurrence of this disease after the epidemic of bovine spongiform encephalopathy (BSE) in cattle.

Methods Case ascertainment of CJD was mostly by direct referral from neurologists and neuropathologists. Death certificates on which CJD was mentioned were also obtained. Clinical details were obtained for all referred cases, and information on potential risk factors for CJD was obtained by a standard questionnaire administered to patients' relatives. Neuropathological examination was carried out on approximately 70% of suspect cases. Epidemiological studies of CJD using similar methodology to the UK study have been carried out in France, Germany, Italy, and the Netherlands between 1993 and 1995.

Findings Ten cases of CJD have been identified in the UK in recent months with a new neuropathological profile. Other consistent features that are unusual include the young age of the cases, clinical findings, and the absence of the electroencephalogram features typical for CJD. Similar cases have not been identified in other countries in the European surveillance system.

Interpretation These cases appear to represent a new variant of CJD, which may be unique to the UK. This raises the possibility that they are causally linked to BSE. Although this may be the most plausible explanation for this cluster of cases, a link with BSE cannot be confirmed on the basis of this evidence alone. It is essential to obtain further information on the current and past clinical and neuropathological profiles of CJD in the UK and elsewhere.

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Introduction

Because of the epidemic of bovine spongiform encephalopathy (BSE) in cattle, surveillance of Creutzfeldt-Jakob disease (CJD) in the UK was reinstituted in May, 1990. The purpose of the surveillance is to identify changes in the pattern of CJD which might indicate an association with BSE. We report ten cases of CJD in the UK with clinical onset of disease in 1994 and 1995. These cases all have neuropathological changes which, to our knowledge, have not been previously reported. They are also unusual in that they occurred in relatively young people, and the clinical course was not typical of cases of sporadic CJD in the UK.

Methods

Since May, 1990, cases of CJD have been identified to the CJD Surveillance Unit, usually by direct referral from professional groups, which include neurologists and neuropathologists. All death certificates in the UK on which CJD is mentioned are obtained and some cases are identified retrospectively in this way; some are identified from other sources. Clinical details are obtained for all cases, and information on potential risk factors for CJD is obtained with a standard questionnaire, usually administered to a close relative of the case. After obtaining informed consent from the relatives or patients, blood is obtained for DNA analysis in most patients. Information on all known cases of CJD in England and Wales since 1970 and in Scotland and Northern Ireland since 1985 is also available from previous surveys of CJD.[1] Parallel studies of CJD have been carried out in France, Italy, Germany, and the Netherlands between 1993 and 1995 with similar methods.[2]

Whenever possible, neuropathological examination is carried out on cases and suspect cases notified to the CJD Surveillance Unit. Such examinations have been done on about 70% of cases notified since May, 1990, either by referral for necropsy in Edinburgh or in cooperation with neuropathologists in other centres who refer cases after diagnosis. Blocks from the frontal, temporal, parietal, and occipital cortex; basal ganglia; thalamus; hypothalamus; cerebellum midbrain; pons; and medulla are fixed in formalin. Blocks are immersed in 96% formic acid for 1 hour before routine processing into paraffin wax. Sections are cut at 5μm and stained by conventional histological techniques and immunocytochemistry for prion protein (PrP). Pretreatments for immunocytochemistry with two monoclonal PrP antibodies (KG9 and 3F4)[3] include incubation in 96% formic acid for 5 min, then 4 mol/L guanidine thiocyanate for 2 hours, and hydrated autoclaving at 121°C for 10 min.

Results

Patients

Of the 207 cases of CJD examined neuropathologically since May, 1990, ten have neuropathological findings that clearly distinguish them from other cases examined by the CJD Surveillance Unit (two have been reported previously[4,5]).

These ten cases (four male) had disease onset from

	<30	30–34	35–39	40–44
1970–79	0	2	3	2
1980–84	1	1	3	1
1985–89	0	0	3	3
1990–94	0	0	1§	2
1995–96‡	5 (1)	2 (1)	0	1

*Excludes known iatrogenic and inherited cases. †England and Wales only for the period 1970–84. ‡Numbers in brackets indicate patients alive. §Died before May 1990.

Table 1: **Known cases of sporadic CJD* in the UK,† 1970–96, dying aged less than 45 years**

February, 1994, to October, 1995. One came to the attention of the CJD Surveillance Unit in March, 1995, and the other nine between October, 1995, and January, 1996. The ages at death of the eight patients who have died range from 19 to 41 years (median 29). Two patients remain alive at ages 18 and 31 years. Intervals between disease onsets and death range from 7·5 to 22·5 months (median 12). Surviving patients in March, 1996, have disease durations of 6 and 22 months. These patients are relatively young compared with most patients with CJD and their disease duration is relatively long. Among 185 cases of sporadic CJD identified since May, 1990, average age at onset was 65 years and median duration of disease four months; for half of these patients, duration was 2½ to 6½ months. Since May, 1990, only two other sporadic cases of CJD with age less than 45 years have been identified, both aged 44 years. These cases had disease onsets in 1993 and 1994; neither showed the neuropathological changes described.

Table 1 shows the cases of CJD dying in England and Wales between 1970 and 1984 and in the UK from 1985 to 1996 at age less than 45 years. Six cases of CJD aged less than 30 years and three aged 30 to 34 years have been identified since 1990—all these cases were identified within the last 10 months. In comparison only one case of CJD aged less than 30 years and three aged 30 to 34 years were identified between 1970 and 1989. We have been able to examine pathological material from one of these earlier cases which did not show the neuropathological pattern described in this report and in the three other caes review of neuropathological reports did not suggest this pattern.

Clinical course

The clinical course of disease in the ten patients was distinct from that usually seen in sporadic CJD (table 2). Nine had behavioural changes as an early clinical feature and were referred to a psychiatrist. In four patients, an early symptom was dysaesthesiae and in another, pain in the feet persisted throughout the illness. Nine patients developed ataxia early in the course of the disease. While all patients developed progressive dementia, in only two was memory impairment part of initial clinical presentation. Seven of the patients developed myoclonus, often late in the course of the disease, and three had choreoathetosis. None of the cases had the electroencephalographic (EEG) features usually associated with CJD.

With established diagnostic criteria for CJD,[6] none of these cases would have been classified as "probable" cases of CJD on clinical grounds. At the time of initial referral to the CJD Surveillance Unit, two patients were classified as definite cases (after brain biopsy) and another as a possible case, while the remaining seven did not fulfil the criteria for even "possible" CJD.

Information on PrP genotype is available for eight cases. All were methionine homozygotes at codon 129 of the PrP gene and none of the known mutations associated with the inherited forms of CJD was identified. In a study of codon 129 genotypes in sporadic CJD in the UK, 1990–93, 83% of cases (n=111) were methionine homozygotes.

Neuropathological features

Neuropathological examination in all ten cases showed spongiform change and PrP plaques confirming the diagnosis of CJD.[6] In two cases investigated by cerebral biopsy and in the eight necropsy cases, neuropathological features were uniform, with spongiform change in a relatively sparse distribution throughout the cerebral cortex (although all areas were involved to a variable extent in each case who came to necropsy). Spongiform change, neuronal loss, and astrocytosis were most evident in the basal ganglia and thalamus, and were present focally in the cerebrum and cerebellum, most evidently in areas with confluent spongiform change.

The most striking and consistent neuropathological abnormality in all cases was PrP plaques. In the eight necropsy cases, plaques were extensively distributed throughout the cerebrum and cerebellum, with smaller numbers in the basal ganglia, thalamus, and hypothalamus. Many of these plaques resembled kuru-type plaques with a dense eosinophilic centre and pale periphery and, unusually for this type of lesion, were surrounded by a zone of spongiform change (figures 1 and 2). This unusual feature was not seen in any of the other 175 sporadic CJD cases investigated. Similar lesions have, however, been described in scrapie, where they have been referred to as "florid" plaques.[7] Immunocytochemistry for PrP showed strong staining of these plaque-like lesions, but also showed many other smaller plaques, which appeared both as single and multicentric deposits. PrP deposition was also seen in a pericellular distribution in the cerebral cortex and in the molecular layer of the cerebellum, the pattern of which suggested deposition

Age at onset	Sex	Year of onset	Year of death	Duration of illness (months)	Presenting symptom	Psychiatric symptoms	Ataxia	Dementia	Myoclonus
16*	F	1994	Alive	>22	Dysaesthesiae	+	+	+	+
18*	M	1994	1995	11	Behavioural change	+	+	+	+
19	M	1995	1996	13	Personality change	+	+	+	
26	F	1994	1996	22·5	Dysaesthesiae	+	+	+	+
28*	F	1995	1996	10	Memory impairment	+	+	+	+
28	F	1995	1995	11	Behavioural change	+	+	+	+
29	F	1994	1996	17	Depression	+	+	+	
29	M	1995	1995	7·5	Foot pain	+	+	+	+
31	M	1995	Alive	>6	Memory impairment	+	+	+	
39	F	1994	1996	21	Dysaesthesiae	+	+	+	+

*Already published (references 4, 5, and 18).

Table 2: **Characteristics of ten cases of CJD in the UK**

around small neurons (figure 3). Plaque and pericellular PrP deposits occurred throughout the cerebrum and cerebellum, and were clearly visible in the absence of confluent spongiform change in the surrounding neuropil. In the basal ganglia and thalamus, a perivacuolar pattern of PrP staining was also seen, with linear tract-like deposits within the grey matter. PrP plaques were also noted in these regions although there were fewer than in the cerebrum and cerebellum (figure 4).

These qualitative differences in the nature of the neuropathological lesions and morphology of PrP deposits were matched by an apparent increase in the amount of PrP deposited in all grey-matter regions compared with sporadic cases, 12 iatrogenic cases, six cases of inherited CJD, and in four cases of Gerstmann-Straussler-Scheinker syndrome.

Risk factors

Information on potential risk factors for CJD is available for nine cases. None had a history of potential iatrogenic exposure to CJD through neurosurgery or human-pituitary-derived hormones, and none had had a blood transfusion. Four cases had no history of any operation, four had undergone minor surgery (two tonsillectomy in 1975 and 1991, one a foot operation in 1984, one a dilatation and curetage in 1989), and one had had a caesarean section (1974), colonoscopy (1992, 1994), and laparoscopy (1986). One patient had worked as a butcher from 1985 to 1987 and another had visited an abattoir for two days in 1987. None had ever worked on farms with livestock, although one patient had spent 1 week's holiday a year on a dairy farm between 1976 and 1986. There was no record of BSE in this herd. All nine cases were reported to have eaten beef or beef products in the last 10 years, but none was reported to have eaten brain. One of the cases had been a strict vegetarian since 1991.

Discussion

The ten cases of CJD in this report are remarkable in that they have a specific neuropathological profile which, to our knowledge, has not been described previously[4,5] and which is so consistent that neuropathological samples from the cases are virtually indistinguishable. The cases are further characterised by having remarkably low ages at onset for CJD and other atypical features, including a generally protracted and unusual clinical course and absence of EEG changes typical of CJD. These findings raise the possibility that the cases represent a new clinicopathological variant of CJD.

Effect of age

It is possible that the unusual neuropathological profile of these cases is due to their young age. Review of published reports on previous young patients worldwide did not reveal any descriptions of neuropathology similar to these

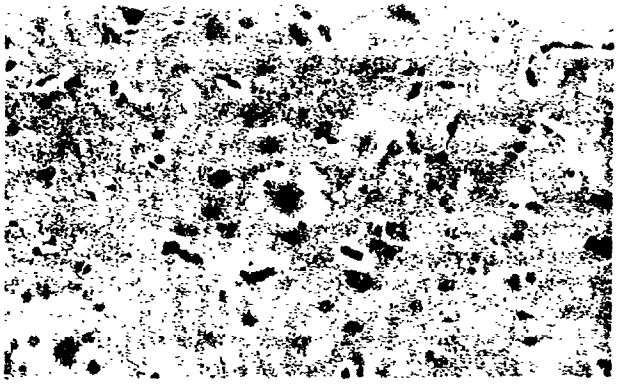

Figure 1: **Large kuru-type plaque surrounded by a zone of spongiform change in a cerebral cortical-biopsy specimen (centre). A smaller plaque is also present (right) but spongiform change is sparse**
Haematoxylin and eosin.

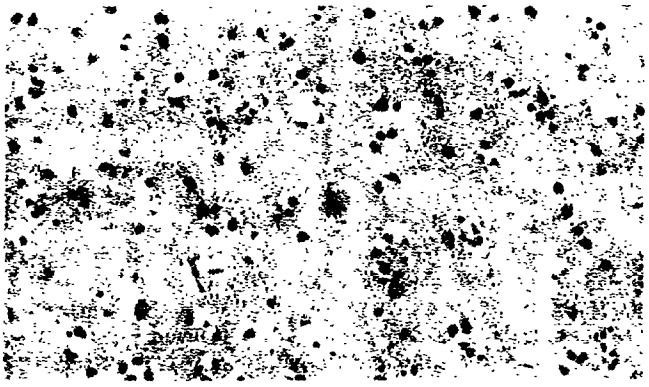

Figure 2: **Cerebral cortex in a case at necropsy with a large kuru-type plaque surrounded by spongiform change (centre) with smaller lesions present in the surrounding neuropil (right and below)**
Haematoxylin and eosin.

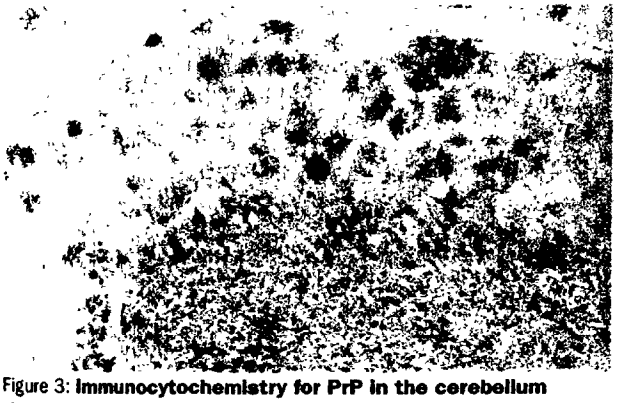

Figure 3: **Immunocytochemistry for PrP in the cerebellum shows strong staining of a kuru-type plaque (centre) with multiple smaller plaques in the granular layer and abundant pericellular deposition in the molecular layer**

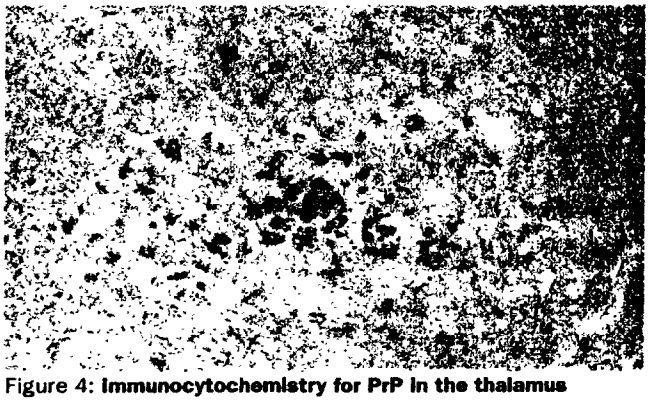

Figure 4: **Immunocytochemistry for PrP in the thalamus shows several large multicentric plaques (centre) with perivacuolar and synaptic deposition in the surrounding neuropil**

UK cases. In 14 cases of CJD aged less than 30 years previously reported outside the UK, plaques are described in only one, and in this report the possible diagnosis of Gerstmann-Straussler-Scheinker syndrome was raised. In four of these cases,[9-12] pathological reports have been reviewed and there was no evidence of PrP plaques (Paul Brown, personal communication). We did immunocytochemical staining on another of these cases of CJD aged 27 years from Poland (courtesy of Professor Kulczycki) and on a 16-year-old patient from the UK dying of CJD in 1980, and there was no evidence of plaque formation in either case. We also did immunocytochemical staining on 11 cases of CJD developing after administration of human growth hormone (mean age 27·5 years) and although PrP plaques were present predominantly in the cerebellum, the neuropathological features in these cases[13] were otherwise quite distinct from the young patients in this report. We emphasise that plaque distribution and spongiform change in these ten young cases were clearly apparent on routine light microscopy. Current evidence suggests, therefore, that the pathological profile in these cases is unlikely to be simply an age-related feature.

CJD has been described previously in young patients, but these are usually isolated case reports[9-12] and in systematic surveys the identification of CJD in patients aged less than 30 years old is exceptional. In the UK, only one such case was identified between 1970 and 1989. In France, between 1968 and 1982,[14] only two patients aged less than 30 years old were identified; only one was identified in Japan between 1975 and 1977; and none at all in Israel between 1963 and 1987. Additional cases aged less than 40 years have been identified through the European surveillance project on CJD (1993–95); two cases aged 22 and 34 years old were found in the Netherlands; two aged 31 and 33 years old in Germany; two aged 26 and 37 years old in France; and one aged 37 years old in Italy. Six of these cases are judged on clinical evidence not to be similar to the cases described in this report. Neuropathological information is available on two of these six cases, neither of which showed the characteristic changes. In the remaining case, full neuropathological information will be available shortly.

Case ascertainment

The overall incidence of CJD has risen in the UK in the 1990s,[15] although this is due mainly to an increase in the incidence of CJD in those aged over 75 years (these cases have a typical clinicopathological profile). The most likely explanation for this is improved ascertainment of CJD in the elderly, with the possible implication that the identification of young cases of CJD may be due to similar improved case ascertainment due in part to the publicity surrounding the BSE epidemic. It is noteworthy that three of the ten cases in this report were notified to the CJD Surveillance Unit as suspect cases of CJD only after biopsy samples had been examined. In the absence of neuropathological examination, these cases might not have come to the attention of the CJD Surveillance Unit. It seems likely, however, that patients of this age dying of a progressive neurological condition would have undergone necropsy in the past. Two cases came to the attention of the CJD Surveillance Unit through unconventional means (through a newspaper report and after a clinical presentation of other cases) which led to their notification earlier than would otherwise have been the case. All of the ten cases were identified over 10 months and although there was extensive publicity surrounding two young cases in late 1995, there has been considerable publicity regarding CJD and BSE since 1990. Other European countries have undertaken systematic surveillance of CJD over a similar period and there has been no obvious increase in the incidence of CJD in young patients despite detailed investigation.

There is a possibility that the diagnosis of such atypical cases may previously have been previously missed. Three of the 14 cases discussed above were from Poland, aged 19, 23, and 27 years, and were identified in the course of a study of subacute sclerosing panencephalitis (SSPE).[16] A recent review of the clinical details of suspect but unconfirmed cases of SSPE held by the SSPE register in the UK has provided no evidence that cases of CJD were misdiagnosed as SSPE in the UK. Although improved ascertainment remains a potential explanation for the identification of the young patients we report, such information as is available does not support this interpretation.

Possible link with BSE

The first aim of the CJD Surveillance Unit has been to identify any changes in CJD that might be attributable to the transmission of BSE to the human population. Although the small number of cases in this report cannot be regarded as proof, the observation of a potentially new form of CJD in the UK is consistent with such a link. The common neuropathological picture may indicate infection by a common strain of the causative agent, as in sheep scrapie in which strains of the disease have been identified which can be distinguished on the basis of disease-incubation period and distinctive neuropathological profile in mouse models.[17] Exposure of the human population to the BSE agent is likely to have been greatest in the 1980s, and especially towards the end of that decade, before the ban on the use of specified bovine offal was introduced. This would be consistent with an incubation period of between 5 and 10 years for these cases.

If the present cases are due to exposure to the BSE agent and this accounts for the distinctive neuropathological appearance, it is not clear why this previously unrecognised variant of the disease has been found only in persons under the age of 45 years. The absence of this variant in older persons could be due to age-related exposure to the agent; to reduced susceptibility among older persons; or to misdiagnosis of this variant of the disease in older age-groups, especially in those in which dementia is more common.

We were alerted earlier to a possible link between CJD and BSE by our finding of an apparent excess of CJD among cattle farmers.[15] Our interpretation of this was tempered by observations of high rates among cattle farmers in other European countries in which BSE was either very rare or had not been reported. None of the four farmers showed the neuropathological features described here, and all were consistent with previous experience of sporadic cases of CJD.

Conclusions

We believe that our observation of a previously unrecognised variant of CJD occurring, to date, only in persons under the age of 45 years is a cause for great concern. That it is due to exposure to the BSE agent is

perhaps the most plausible interpretation of our findings. However, we emphasise that we do not have direct evidence of such a link and other explanations are possible. That these cases have been observed now because of improved ascertainment cannot be completely dismissed. It seems unlikely, however, that such a distinctive neuropathological pattern would have been missed previously, especially among persons dying at a young age. It is essential to obtain information on the clinical and neuropathological characteristics of young patients with CJD in Europe and elsewhere, and historically in the UK, but proof of an association between BSE and CJD may depend on animal transmission studies and continued epidemiological vigilance. If there is a causal link then, given the potentially long and widespread exposure to the BSE agent, further cases of this new variant of CJD are likely to arise.

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